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Remarks:

The applicant has subsequently filed a sequence listing and declared, that it includes no new matter.

(54) **Gonadotropin receptor**

(57) The present invention relates to newly identified DNA sequences which code for novel gonadotropin receptors, as well as to the complete genes and the encoded proteins. The invention furthermore relates to a method for identification of molecules able to bind to these receptors. The invention can be used for the development of new drugs for treatment of infertility or for contraception.

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Description

[0001] The present invention relates to newly identified DNA sequences which code for novel gonadotropin receptors, as well as to the complete genes and the encoded proteins. The invention furthermore relates to a method for identification of molecules able to bind to these receptors or specific domains thereof. The invention therefore has useful applications in fields including basic biomedical and biochemical research and drug development.

[0002] Gonadotropins act on specific gonadal cell types to initiate ovarian and testicular differentiation and steroidogenesis. The actions of these pituitary and placental hormones are mediated by specific plasma membrane receptors that are members of the large family of G-protein coupled receptors. They consist of a single polypeptide with seven transmembrane domains and are able to interact with the G_s protein, leading to the activation of adenylyl cyclase.

[0003] Isolation of the FSH, LH and TSH receptor (hereafter called gonadotropin receptors) cDNAs indicates that these glycoprotein hormone receptors are homologous in their transmembrane regions, but have long and divergent extracellular domains resembling proteins of the leucine-rich protein family (Tilly et al, 1992, *Endocrinol.*, 131, 799-806; Parmentier et al, 1989, *Science*, 246, 1620-1622; Jia et al, 1991, *Mol. Endocrinol.*, 5, 759-768).

[0004] There are several indications pointing to the presence, next to the FSH, LH and TSH receptor, of an additional glycoprotein receptor in the human body. Blithe et al, (1991, *Endocrinol.*, 129, 2257-2259) have suggested a specific role for α -hCG during pregnancy that can not be exerted by the hCG dimer, namely stimulation of prolactin (PRL) secretion from term pregnancy decidual cells. PRL appears to be involved in endometrial cell proliferation and attachment (Negami and Tominaga, 1991, *Horm. Res. [Suppl.]*, 35, 50-57). Since the free α -subunit of hCG is not able to elicit a biological response via the LH/CG receptor, the involvement of a novel glycoprotein receptor is very likely. Moreover, *in vitro* the α -subunit acts synergistically with progesterone to induce decidualisation of human endometrial stromal cells (Moy et al, 1996, *Endocrin.*, 137, 1332-1339). Decidual cells are important for implantation and provide nutritional support for the embryo.

[0005] Furthermore, in GnRH-antagonist treated female cyclic rats hCG and LH preparations induce ovulation at a similar dose-level. However, in the hCG treated animals embryo implantation is negatively effected whereas, in contrast, LH treated animals show normal implantation. Preliminary experiments indicate that this different effect on implantation is only partly caused by the different half-life of hCG and LH. The uterus and the ovary, therefore, may contain LH/CG receptors with a different affinity for hCG and LH i.e. a novel glycoprotein receptor.

[0006] At present, however, only the nucleotide sequences of the human FSH, LH and TSH receptors have been elucidated and no direct data confirming the presence of additional gonadotropin receptors have been obtained. It will be clear that there is a great need for the elucidation of other receptors, in order to unravel the various roles these receptors play in normal physiology and pathology.

[0007] A better knowledge of these receptors, their mechanism of action and of the ligands which bind to these receptors might help to create a better insight in the underlying mechanism of the hormone signal transduction pathway, which eventually will lead to better treatment of fertility associated diseases and abnormalities linked to suboptimal hormone/receptor functioning.

[0008] The present invention provides for such novel receptors. More specific, the present invention provides for polynucleotide sequences comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 or nucleotides 2-1487 of SEQ ID NO:7 or nucleotides 1-2541 of SEQ ID NO:9.

[0009] The sequences of the present invention can be used as probes or as a source to prepare synthetic oligonucleotides to be used as primers in DNA amplification reactions allowing the isolation and identification of the complete gene. The complete genetic sequence can be used in the preparation of vector molecules for expression of the protein in suitable host cells.

[0010] Using the sequence information provided herein, complete genes or variants thereof can be derived from cDNA or genomic DNA from natural sources or synthesized using known methods.

[0011] Thus, an additional embodiment of the invention is a method to isolate a gene comprising the steps: a) hybridizing a DNA according to the present invention under stringent conditions against nucleic acids being RNA, (genomic) DNA or cDNA isolated preferably from tissues which highly express the DNA of interest; and b) isolating said nucleic acids by methods known to a skilled person in the art. The tissues preferably are from human origin. Preferably ribonucleic acids are isolated from reproductive tissues, preferably ovary, testis or uterus.

[0012] The hybridization conditions are preferably highly stringent.

[0013] According to the present invention the term "stringent" means washing conditions of 1 x SSC, 0.1% SDS at a temperature of 65 °C; highly stringent conditions refer to a reduction in SSC towards 0.3 x SSC.

[0014] Thus, the invention also includes the entire coding sequence part of which is indicated in SEQ ID NOs: 1, 2, 3, 7, 11, 12 or 13. A complete sequence is shown in SEQ ID NO:9. Furthermore, to accommodate codon variability, the invention also includes sequences coding for the same amino acid sequences as the sequences disclosed herein. Also portions of the coding sequences coding for individual domains of the expressed protein are part of the invention as well as allelic and species variations thereof. Sometimes, a gene is expressed in a certain tissue as a splicing variant, result-

ing in an altered 5' or 3' mRNA or the inclusion of an additional exon sequence. Alternatively, the messenger might have an exon less as compared to its counterpart as indicated in one of the sequences enlisted here. These sequences as well as the proteins encoded by these sequences all are expected to perform the same or similar functions and form also part of the invention.

5 [0015] The sequence information as provided herein should not be so narrowly construed as to require inclusion of erroneously identified bases. The specific sequence disclosed herein can be readily used to isolate the complete genes which in turn can easily be subjected to further sequence analyses thereby identifying sequencing errors.

[0016] Thus, in one aspect, the present invention provides for isolated polynucleotides encoding a novel gonadotropin receptor.

10 [0017] The DNA according to the invention may be obtained from cDNA. Alternatively, the coding sequence might be genomic DNA, or prepared using DNA synthesis techniques. The polynucleotide may also be in the form of RNA. If the polynucleotide is DNA, it may be in single stranded or double stranded form. The single strand might be the coding strand or the non-coding (anti-sense) strand.

15 [0018] The present invention further relates to polynucleotides which have at least 80%, preferably 90% and more preferably 95% and even more preferably at least 98% identity with SEQ ID NOs:1, 2, 3, 7, 9, 11, 12 or 13 or with nucleotides 2-1487 of SEQ ID NO:7 or 1-2541 of SEQ ID NO:9. Such polynucleotides encode polypeptides which retain the same biological function or activity as the natural, mature protein. Alternatively, also fragments of the above mentioned polynucleotides which code for domains of the receptor proteins which still are capable of binding to ligands are embodied in the invention.

20 [0019] The percentage of identity between two sequences can be determined with programs such as DNAMAN (Lynnon Biosoft, version 3.2). Using this program two sequences can be aligned using the optimal alignment algorithm of Smith and Waterman (1981, J. Mol. Biol., 147:195-197). After alignment of the two sequences the percentage identity can be calculated by dividing the number of identical nucleotides between the two sequences by the length of the aligned sequences minus the length of all gaps.

25 [0020] The DNA according to the invention will be very useful for *in vivo* or *in vitro* expression of the novel receptor proteins according to the invention in sufficient quantities and in substantially pure form.

[0021] In another aspect of the invention, there is provided for a gonadotropin receptor comprising the amino acid sequence encoded by the above described DNA molecules.

30 [0022] Preferably, the gonadotropin receptor according to the invention comprises an amino acid sequence shown in SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:15 or SEQ ID NO:16.

[0023] The receptor according to the invention furthermore distinguishes itself from the other known gonadotropin receptors in differences in tissue distribution, indicating that there may be important differences between these tissues at the level of gonadotropin intermediated signaling.

35 [0024] All novel receptors are expressed in one or more reproductive tissues. Expression of SEQ ID NO:1 is observed in a limited number of tissues, including male but not female reproductive organs. SEQ ID NO:7 and SEQ ID NO:9 are extensions of SEQ ID NO:1. SEQ ID NO:3 is also expressed in a limited number of tissues but prominent expression is found in ovary. In contrast, SEQ ID NO:2 is expressed in the majority of tissues tested, including ovary, testis and uterus.

40 [0025] The identification of additional gonadotropin receptors could be a major step forward to the existing clinical therapies based on the existence of the known gonadotropin receptors as all gonadotropin mediated abnormalities and/or diseases are ascribed to these receptors. The receptors according to the invention will be useful in the development of hormone analogs that selectively activate either one of the classical gonadotropin receptors or the novel receptor according to the invention. This should be considered as one of the major advantages of the present invention.

45 Alternatively, also analogs can be detected which inhibit the receptor function.

[0026] Thus, the invention will facilitate better treatment of fertility associated diseases and/or the design of new drugs for contraception.

[0027] Also functional equivalents that is receptors comprising SEQ ID NOs:4, 5, 6, 8, 10, 14, 15, 16 or parts thereof having variations of the sequence while still maintaining functional characteristics, are included in the invention.

50 [0028] The variations that can occur in a sequence may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence. Amino acid substitutions that are expected not to essentially alter biological and immunological activities, have been described. Amino acid replacements between related amino acids or replacements which have occurred frequently in evolution are, inter alia Ser/Ala, Ser/Gly, Asp/Gly, Asp/Asn, Ile/Val (see Dayhof, M.D., Atlas of protein sequence and structure, Nat. Biomed. Res. Found., Washington D.C., 1978, vol. 5, suppl. 3). Based on this information Lipman and Pearson developed a method for rapid and sensitive protein comparison (Science, 1985, 227, 1435-1441) and determining the functional similarity between homologous polypeptides. It will be clear that also polynucleotides coding for such variants are part of the invention.

[0029] The polypeptides according to the present invention include the polypeptides comprising SEQ ID NOs:4, 5, 6, 8, 10, 14, 15 or 16 but also polypeptides with a similarity of 70%, preferably 90%, more preferably 95%. Also portions of such polypeptides still capable of conferring biological effects are included. Especially portions which still bind to ligands form part of the invention. Such portions may be functional per se, e.g. in solubilized form or they might be linked to other polypeptides, either by known biotechnological ways or by chemical synthesis, to obtain chimeric proteins. Such proteins might be useful as therapeutic agent by preventing the ligand from interacting with the natural gonadotropin receptors in the body.

[0030] Alternatively, downregulation of the expression level of the receptor can be obtained by using anti-sense nucleic acids through triple-helix formation (Cooney et al., 1988, Science, 241, 456-459) or by binding to the mRNA. This in itself could also lead to treatment of infertility or to contraception.

[0031] A wide variety of host cell and cloning vehicle combinations may be usefully employed in cloning the nucleic acid sequence coding for the receptor the ligand-binding domain of the invention. For example, useful cloning vehicles may include chromosomal, non-chromosomal and synthetic DNA sequences such as various known bacterial plasmids and wider host range plasmids and vectors derived from combinations of plasmids and phage or virus DNA.

[0032] Vehicles for use in expression of the receptor or ligand-binding domain thereof of the present invention will further comprise control sequences operably linked to the nucleic acid sequence coding for the ligand-binding domain. Such control sequences generally comprise a promoter sequence and sequences which regulate and/or enhance expression levels. Of course control and other sequences can vary depending on the host cell selected.

[0033] Suitable expression vectors are for example bacterial or yeast plasmids, wide host range plasmids and vectors derived from combinations of plasmid and phage or virus DNA. Vectors derived from chromosomal DNA are also included. Furthermore an origin of replication and/or a dominant selection marker can be present in the vector according to the invention. The vectors according to the invention are suitable for transforming a host cell.

[0034] Recombinant expression vectors comprising the DNA of the invention as well as cells transformed with said DNA or said expression vector also form part of the present invention.

[0035] Suitable host cells according to the invention are bacterial host cells, yeast and other fungi, plant or animal host such as Chinese Hamster Ovary cells or monkey cells. Thus, a host cell which comprises the DNA or expression vector according to the invention is also within the scope of the invention. The engineered host cells can be cultured in conventional nutrient media which can be modified e.g. for appropriate selection, amplification or induction of transcription. The culture conditions such as temperature, pH, nutrients etc. are well known to those ordinary skilled in the art.

[0036] The techniques for the preparation of the DNA or the vector according to the invention as well as the transformation or transfection of a host cell with said DNA or vector are standard and well known in the art, see for instance Sambrook et al., *Molecular Cloning: A laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989.

[0037] The proteins according to the invention can be recovered and purified from recombinant cell cultures by common biochemical purification methods including ammonium sulfate precipitation, extraction, chromatography such as hydrophobic interaction chromatography, cation or anion exchange chromatography or affinity chromatography and high performance liquid chromatography. If necessary, also protein refolding steps can be included.

[0038] Gonadotropin hormone receptors according to the present invention can be used for the *in vitro* or *in vitro* identification of novel ligands or hormonal analogs. For this purpose binding studies can be performed with cells transformed with DNA according to the invention or an expression vector comprising DNA according to the invention, said cells expressing the gonadotropin receptor according to the invention.

[0039] Alternatively also the novel purified hormone receptor according to the invention as well as the ligand-binding domain thereof can be used in an assay for the identification of functional ligands or hormone analogs for the receptor.

[0040] Methods to determine receptor binding as well as *in vitro* and *in vivo* assays to determine biological activity of gonadotropins are well known. In general, expressed receptor is contacted with the compound to be tested and binding, stimulation or inhibition of a functional response is measured.

[0041] Thus, the present invention provides for a method for identifying ligands for gonadotropin receptors according to the invention, said method comprising the steps of:

- introducing into a suitable host cell a DNA or an expression vector according to the invention,
- culturing cells under conditions to allow expression of the DNA sequence
- optionally isolating the expression product
- bringing the expression product (or the host cell from the second step) into contact with potential ligands which will possibly bind to the ligand-binding domain of the receptor protein encoded by said DNA from the first step;
- establishing the amount of binding of the ligand to the receptor.

[0042] As an alternative to the binding of the ligand to the receptor also signal transduction capacity may be established.

[0043] SEQ ID NO:8 comprises the C-terminal part of the receptor, including all its transmembrane domains. This part is encoded by the nucleic acid of SEQ ID NO:7 from nucleotide 2-1487. This polypeptide part can also be used in a similar screenings assay to detect low molecular weight compounds by binding or by measuring the second messenger levels. Another part of this receptor is indicated in SEQ ID NO:4 and is encoded by SEQ ID NO:1. The complete sequence of this receptor is shown in SEQ ID NO:10 and is encoded by the nucleotides 1-2541 of SEQ ID NO:9. The polypeptide of SEQ ID NO:6 is encoded by SEQ ID NO:3. SEQ ID NO:5, SEQ ID NO:14, SEQ ID NO 15 and SEQ ID NO 16 all belong to the same receptor ad are encoded by SEQ ID NO:2, SEQ ID NO:11, SEQ ID NO 12 and SEQ ID NO 13, respectively.

[0044] The present invention thus provides for a quick and economic method to screen for therapeutic agents for the prevention and/or treatment of diseases related to reproductive tissues or for contraception. The method according to the invention furthermore provides for the selection of selective therapeutic agents discriminating between different gonadotropin receptors thus leading to a more effective therapeutic agent and/or diminishing of side effects. The method is especially suited to be used for the high through put screening of numerous potential compounds.

[0045] Compounds which activate or inhibit the receptor function may be employed in therapeutic treatments to activate or inhibit the receptors of the present invention.

[0046] Also within the scope of the invention are antibodies, especially monoclonal antibodies raised against the receptor molecule according to the invention. Such antibodies can be used therapeutically to inhibit receptor function and diagnostically to detect receptor molecules.

[0047] The invention furthermore relates to the use of the receptor genes as part of a diagnostic assay for detecting fertility abnormalities or susceptibility to infertility related to mutations in the nucleic acid sequences encoding these receptors. Such mutations may e.g. be detected by using PCR (Saiki et al., 1986, Nature, 324, 163-166). Also the relative levels of RNA can be determined using e.g. hybridization or quantitative PCR technology. The presence and the levels of the receptors themselves can be assayed by immunological technologies such as radioimmuno assays, Western blots and ELISA using specific antibodies raised against the receptor. Such techniques for measuring RNA and protein levels are well known to the skilled artisan.

[0048] The determination of expression levels of different receptors in individual patients may lead to fine tuning of treatment protocols.

[0049] The following examples are illustrative for the invention and should in no way be interpreted as limiting the scope of the invention.

Legends to the figures

Figure 1

Nothern blot of sequence SEQ ID NO:1

[0050] X-ray autoradiograph of a multiple tissue Northern blot type II (Clontech) hybridized with a ³²P labeled probe obtained from SEQ ID NO 1. The lanes contain poly A⁺ RNA from the following human tissues/cell-types: spleen (1), thymus (2), prostate (3), testis (4), ovary (5), small intestine (6), colon (7) and peripheral blood leukocytes (8).

Figure 2

Nothern blot of sequence SEQ ID NO:2

[0051] X-ray autoradiograph of a multiple tissue Northern blot type II and IV (Clontech) hybridized with a ³²P labeled probe obtained from SEQ ID NO:2. The lanes contain poly A⁺ RNA from the following human tissues/cell-types: spleen (1), thymus (2), prostate (3), testis (4), ovary (5), small intestine (6), colon (7), peripheral blood leukocytes (8) and uterus (9).

Figure 3

Nothern blot of sequence SEQ ID NO:3

[0052] X-ray autoradiograph of a multiple tissue Northern blot type II (Clontech) hybridized with a ³²P labeled probe obtained from SEQ ID NO 3. The lanes contain poly A⁺ RNA from the following human tissues/cell-types: spleen (1), thymus (2), prostate (3), testis (4), ovary (5), small intestine (6), colon (7) and peripheral blood leukocytes (8).

Examples**Example 1****5 Sequence Identification**

[0053] Using parts of the DNA sequence and/or the protein sequence of the human gonadotropin receptors and receptors from evolutionary distant organisms, we have screened several databases for the presence of related human (partial) cDNA sequences. The identified cDNA clones were obtained from several tissues and sequenced using an automatic sequencer. Three cDNA clones were obtained encoding parts of the transmembrane domains of three novel human gonadotropin receptors. The sequences are shown in SEQ ID NOs: 1, 2, 3, 7, 9, and 13. SEQ ID NOs 1, 7 and 9 are overlapping sequences. SEQ ID NO:7 contains all transmembrane domains. SEQ ID NO:9 encodes the complete protein. SEQ ID NOs 2, 11, 12 and 13 are part of the same receptor.

The gonadotropin receptors form a well defined family in the very large superfamily of the G-protein coupled receptors. Within this superfamily especially the seven transmembrane domains are relatively good conserved. However, there are specific motif differences between different families. Motifs in the transmembrane domains III and VI are usually very specific for a certain family, and therefore could indicate the probability that a candidate receptor is indeed a member of the family of gonadotropin receptors. Indeed, especially transmembrane domains III is very conserved among the novel receptors comprising SEQ ID NO:2 and 3 and the human gonadotropin receptors. In addition, transmembrane domain VI is very conserved among the receptors comprising SEQ ID NO:1 and SEQ ID NO:2 and the human gonadotropin receptors. Furthermore, the domains III and VI are much less conserved between the novel receptors and human G-protein coupled receptors other than gonadotropin receptors. Thus, it is concluded that the three novel protein sequences are derived from novel gonadotropin receptors.

25 Example 2**Tissue distribution of the expression of gonadotropin receptor no.1**

[0054] In order to analyze the expression of the receptor comprising SEQ ID NO:1 in different human tissues Northern blot analysis was performed. A human Multiple Tissue Northern blot type II was obtained from Clontech, which contains poly A⁺ RNA from the following human tissues/cell-types: spleen (lane 1), thymus (lane 2), prostate (lane 3), testis (lane 4), ovary (lane 5), small intestine (lane 6), colon (lane 7) and peripheral blood leukocytes (lane 8). Prehybridization was performed in hybridization solution (0.5 M Phosphate buffer pH 7.5, 7 % Sodium Dodecyl Sulfate (SDS), 1 mM EDTA) for 1 hour at 65 °C. For RNA detection, ³²P labeled DNA fragments were generated with an Oligolabeling kit (Pharmacia) using a 440 bp fragment from receptor sequence no. 1. This fragment starts at the 5' end of the coding sequence and stops at a Hind III site approximately 440 basepairs downstream (comprising nucleotide no 1 to 426 in SEQ ID NO:1). The ³²P labeled probes were hybridized to the filters for 16 hours at 65 °C. Subsequently, the filters were washed in solutions with decreasing salt concentrations up to 0.3 x SSC + 0.1% SDS at 65 °C and exposed to an X-ray film (X-Omat AR, Kodak).

[0055] From the results shown in Figure 1 it can be concluded that gonadotropin receptor no. 1 is only expressed in a limited number of tissues, namely testis, prostate and spleen. Thus, expression of this receptor is observed in male but not in the female reproductive organs. The length of the mRNA in spleen and prostate is approximately 3.5-4.5 kb, while the length in testis is about 2.5-3.5 kb. In addition, a small mRNA of approximately 0.5-1.0 is observed in several tissues. However, the small length of this transcript suggests that it can not encode a full length gonadotropin receptor.

45 Example 3**Tissue distribution of the expression of gonadotropin receptor no.2**

[0056] In order to analyze the expression of receptor no. 2 (comprising SEQ ID NO:2) in different human tissues Northern blot analysis was performed. Human Multiple Tissue Northern blots type II and IV were obtained from Clontech. Blot type IV is identical to blot type II (see example 2) with the exception that the poly A⁺ RNA obtained from ovary is replaced by poly A⁺ RNA from uterus (number 9). (Pre)hybridization and labeling of the probe was performed as described in example 2. For probe generation a 800 base pair fragment from receptor sequence no. 2 was used. This fragment starts at the 5' end of the coding sequence and stops at a Pvu II site approximately 800 basepairs downstream (comprising nucleotide no 1 to 664 in SEQ ID NO:2 plus in addition approximately 140 basepairs of unknown sequence). The filters were washed in solutions with decreasing salt concentrations up to 0.3 x SSC + 0.1% SDS at 65 °C and exposed to an X-ray film (X-Omat AR, Kodak).

[0057] From the results shown in Figure 2 it can be concluded that gonadotropin receptor no. 2 is expressed in the majority of tissues tested, including ovary, testis and uterus. The length of the mRNA is approximately 5.5-6.5 kilobases.

Example 4

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Tissue distribution of the expression gonadotropin receptor no.3

[0058] In order to analyze the expression of receptor no. 3 (comprising SEQ ID NO:3) in different human tissues Northern blot analysis was performed. The methods used are comparable to those described in example 2. As a probe a 820 base pair fragment from receptor sequence no. 3 was used. This fragment starts at the 5' end of the coding sequence and stops at a Not I restriction enzyme cleavage site (located immediately downstream of the DNA insert within the vector sequence) approximately 820 basepairs downstream (comprising nucleotide no 1 to 606 of SEQ ID NO:3 plus additional approximately 120 basepairs of unknown sequence). The filters were washed in solutions with decreasing salt concentrations up to 1 x SSC + 0.1% SDS at 65 °C and exposed to an X-ray film (BioMax, Kodak).

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15 [0059] From the results shown in Figure 3 it can be concluded that gonadotropin receptor no. 3 is expressed in a limited number of tissues, including ovary. The length of the mRNA is approximately 5-6 kilobases.

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Sequence listing

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(1) GENERAL INFORMATION:

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(i) APPLICANT:

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25

(ii) TITLE OF INVENTION: Novel gonadotropin receptor

(iii) NUMBER OF SEQUENCES: 16

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(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

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(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

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(2) INFORMATION FOR SEQ ID NO: 1:

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 515 base pairs

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(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GA	ACTCCTTC	TGTTTCCTGG	TCGTGGCCGG	TGCCTACATC	AAACTGTACT	GTGACCTGCC	60
15	GCGGGGCGAC	TTTGAGGCCG	TGTGGGACTG	CGCCATGGTG	AGGCACGTGG	CCTGGCTCAT	120
	CTTCGCAGAC	GGGCTCCTCT	ACTGTCCCGT	GGCCTTCCTC	AGCTTTGCCT	CCATGCTGGG	180
	CCTCTTCCCT	GTCACGCCCG	AGGCCGTCAA	GTCTGTCCTG	CTGGTGGTGC	TGCCCCTGCC	240
20	TGCCTGCCTC	AACCCACTGC	TGTACCTGCT	CTTCAACCCC	CACTTCCGGG	ATGACCTTCG	300
	GCGGCTTCGG	CCCCCGCGCAG	GGGACTCAGG	GCCCCTAGCC	TATGCTGCGG	CCGGGGAGCT	360
	GGAGAAGAGC	TCCTGTGATT	CTACCCAGGC	CCTGGTAGCC	TTCTCTGATG	TGGATCTCAT	420
25	TCTGGAAGCT	TCTGAAGCTG	GGCGGCCCCC	TGGGCTGGAG	ACCTATGGCT	TCCCCTCAGT	480
	GACCCTCATC	TCCTGTCAGC	AGCCAGGGGC	CCCCA			515

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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 664 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

GC	AGTGGCTG	CAAAGTAGCT	GGGTTTCTTG	CAGTTTCTC	CTCAGAAAGT	GCCATATTTT	60
50	TATTAATGCT	AGCAACTGTC	GAAAGANGCT	TATCTGCAAA	AGATATAATG	AAAAATGGGA	120

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AGAGCAATCA TCTCAAACAG TTCCGGGTTG CTGCCCTTTT GGCTTTCCTA GGTGCTACAG 180
 TAGCAGGCTG TTTTCCCCTT TTCCATAGAG GGAATATTC TGCATCACCC CTTTGTGTTGC 240
 5 CATTTCCCTAC AGGTGAAACG CCATCATTAG GATTCAGTGT AACGTTAGTG NTATTAANCT 300
 CACTAGCATT TTTATTAATG GCCGTTATCT AACTAAGCT ATACTGCAAC TTGGAAAANG 360
 AGGACCTCTC AGAAAACTCA CAATCTAGCA TGATTAAGCA TGTCGCTTGG CTAATCTTCA 420
 10 CCAATTGCAT CTTTTCTGCT CCTGTGGCGT TTTTTCATT TGCACCATTG ATCACTGCAA 480
 TCTCTATCAG CCCCAGAAATA ATGAAGTCTG TTAATCTGAT ATTTTTCCTA TTGCCTGCTT 540
 GCCTGAATCC AGTCCTGTAT GTTTTCTTCA ACCCAAAGTT TAAAGAAGAC TGGAAGTTAC 600
 15 TGAAGCGACG TGTTACCAAG AAAAGTGGAT CAGTTTCAGT TTCCATCAGT AGCCAAGGTG 660
 GTTG

20 (2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
 25 (A) LENGTH: 606 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
 35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

40 ATTGGAGTGT GGACCATAGC AGTTCTGGCA CTTACTTGTA ATGCTTTGGT GACTTCAACA 60
 GTTTTCAGAT CCCCTCTGTA CATTTCCCCC ATTAAACTGT TAATTGGGGT CATCGCAGCA 120
 GTGAACATGC TCACGGGAGT CTCCAGTGCC GTGCTGGCTG GTGTGGATGC GTTCACTTTT 180
 45 GGCAGCTTTG CACGACATGG TGCCTGGTGG GAGAATGGGG TTGGTTGCCA TGTCATTGGT 240
 TTTTGTCCA TTTTGTCTC AGAATCATCT GTTTTCCTGC TTAATCTGGC AGCCCTGGAG 300
 CGTGGGTTCT CTGTGAAATA TTCTGCAAAA TTTGAAACGA AAGCTCCATT TTCTAGCCTG 360
 50 AAAGTAATCA TTTTGCTCTG TGCCCTGCTG GCCTTGACCA TGGCCGAGT TCCCCTGCTG 420
 GGTGCGAGCA AGTATGGCGC CTCCCCTCTC TGCCTGCCTT TGCCTTTTGG GGAGCCCAGC 480

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ACCATGGGCT ACATGGTCGC TCTCATCTTG CTCAATTCCC TTTGCTTCCT CATGATGACC 540
 ATTGCCTACA CCAAGCTCTA CTGCAATTTG GACAAGGGAG ACCTGGAGAA TATTGGGAC 600
 TGCTCT 606

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 171 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Asn Ser Phe Cys Phe Leu Val Val Ala Gly Ala Tyr Ile Lys Leu Tyr

1 5 10 15

Cys Asp Leu Pro Arg Gly Asp Phe Glu Ala Val Trp Asp Cys Ala Met

20 25 30

Val Arg His Val Ala Trp Leu Ile Phe Ala Asp Gly Leu Leu Tyr Cys

35 40 45

Pro Val Ala Phe Leu Ser Phe Ala Ser Met Leu Gly Leu Phe Pro Val

50 55 60

Thr Pro Glu Ala Val Lys Ser Val Leu Leu Val Val Leu Pro Leu Pro

65 70 75 80

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(i) SEQUENCE CHARACTERISTICS:

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(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

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EP 0 950 711 A2

	Ser Gly Cys Lys Val Ala Gly Phe Leu Ala Val Phe Ser Ser Glu Ser
5	1 5 10 15
	Ala Ile Phe Leu Leu Met Leu Ala Thr Val Glu Arg Xaa Leu Ser Ala
10	20 25 30
	Lys Asp Ile Met Lys Asn Gly Lys Ser Asn His Leu Lys Gln Phe Arg
15	35 40 45
	Val Ala Ala Leu Leu Ala Phe Leu Gly Ala Thr Val Ala Gly Cys Phe
20	50 55 60
	Pro Leu Phe His Arg Gly Glu Tyr Ser Ala Ser Pro Leu Cys Leu Pro
25	65 70 75 80
	Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val Thr Leu Val
30	85 90 95
	Xaa Leu Xaa Ser Leu Ala Phe Leu Leu Met Ala Val Ile Tyr Thr Lys
35	100 105 110
	Leu Tyr Cys Asn Leu Glu Xaa Glu Asp Leu Ser Glu Asn Ser Gln Ser
40	115 120 125
	Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe
45	130 135 140
	Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile
50	145 150 155 160
55	

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5 Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro
165 170 175

10 Leu Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys
180 185 190

15 Phe Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser
195 200 205

20 Gly Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly
210 215 220

(2) INFORMATION FOR SEQ ID NO: 6:

25

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 202 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

45 Ile Gly Val Trp Thr Ile Ala Val Leu Ala Leu Thr Cys Asn Ala Leu
1 5 10 15

50 Val Thr Ser Thr Val Phe Arg Ser Pro Leu Tyr Ile Ser Pro Ile Lys
20 25 30

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EP 0 950 711 A2

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EP 0 950 711 A2

Gly Asp Leu Glu Asn Ile Trp Asp Cys Ser

195

200

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(2) INFORMATION FOR SEQ ID NO: 7:

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1987 base pairs

15

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

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CAAGGCCTCT	GGGCAGTGGG	AGGCTGAAGA	CCTTCACCTT	GATGATGAGG	AGTCTTCAAA	60
AAGGCCCTTG	GGCCTCCTTG	CCAGACAAGC	AGAGAACCAC	TATGACCAGG	ACCTGGATGA	120
GCTCCAGCTG	GAGATGGAGG	ACTCAAAGCC	ACACCCCACT	GTCCAGTGTA	GCCCTACTCC	180
AGGCCCCCTT	AAGCCCTGTG	AGTACCTCTT	TGAAAGCTGG	GGCATCCGCC	TGGCCGTGTG	240
GGCCATCGTG	TTGCTCTCCG	TGCTCTGCAA	TGGACTGGTG	CTGCTGACCG	TGTTGCTGG	300
CGGGCCTGCC	CCCCTGCCCC	CGGTCAAGTT	TGTGGTAGGT	GCGATTGCAG	GCGCCAACAC	360
CTTGACTGGC	ATTTCTGTGT	GCCTTCTAGC	CTCAGTCGAT	GCCCTGACCT	TGGTCAGTT	420
CTCTGAGTAC	GGAGCCCGCT	GGGAGACGGG	GCTAGGCTGC	CGGGCCACTG	GCTTCTTGGC	480
AGTACTTGGG	TCGGAGGCAT	CGGTGCTGCT	GCTCACTCTG	GCCGCAGTGC	AGTGCAGCGT	540
CTCCGTCTCC	TGTGTCCGGG	CCTATGGGAA	GTCCCCCTCC	CTGGGCAGCG	TTCGAGCAGG	600
GGTCCTAGGC	TGCCTGGCAC	TGGCAGGGCT	GGCCGCCGCA	CTGCCCCCTG	CCTCAGTGGG	660
AGAATACGGG	GCCTCCCCAC	TCTGCCTGCC	CTACGCGCCA	CCTGAGGGTC	AGCCAGCAGC	720

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	CCTGGGCTTC ACCGTGGCCC TGGTGATGAT GAACTCCTTC TGTTCCTGG TCGTGGCCGG	780
	TGCCTACATC AAAGTGTACT GTGACCTGCC GCGGGGCGAC TTTGAGGCCG TGTGGGACTG	840
5	CGCCATGGTG AGGCACGTGG CCTGGCTCAT CTTGCGAGAC GGGCTCCTCT ACTGTCCCGT	900
	GGCCTTCCTC AGCTTCGCCT CCATGCTGGG CCTCTCCCT GTCACGCCCG AGGCCGTCAA	960
	GTCTGTCTTG CTGGTGGTGC TGCCCTGCC TGCTGCCTC AACCCTACTGC TGTACCTGCT	1020
10	CTTCAACCCC CACTTCCGGG ATGACCTTCG GCGGCTTCGG CCCCAGCGAG GGGACTCAGG	1080
	GCCCCTAGCC TATGCTGCGG CCGGGGAGCT GGAGAAGAGC TCCTGTGATT CTACCCAGGC	1140
	CCTGGTAGCC TTCTCTGATG TGGATCTCAT TCTGGAAGCT TCTGAAGCTG GCGGGCCCCC	1200
15	TGGGCTGGAA CCTATGGCTC CCCTCAGGAC CCTCATTCTT GTCAGAGCCA GGGGCCCCCA	1260
	GGCTGGAGGG CAGCCATTGT GTAGAGCCAG AGGGGAACCA CTTTGGGAAC CCCCACCCCT	1320
	CCATGGATGG AGAACTGCTG CTGAGGCGAG AGGGATCTAC GCCAGCAGGT GGAGGCTTGT	1380
20	CAGGGGGTGG CGCTTTCAGC CCTCTGGCTT GGCCTTTGCT TCACACGTGT AAATATCCCT	1440
	CCCCATTCTT CTCTTCCCT CTCTTCCCTT TCCTCTCTCC CCCTCGGTGA ATGATGGCTG	1500
	CTTCTAAAAC AAATACAACC AAAACTCAGC AGTGTGATCT ATAGCAGGAT GGGCCAGTAC	1560
25	CTGGCTCCAC TGATCACCTC TCTCCTGTA CCATCACCAA CGGGTGCCCT CTGGGCTGG	1620
	CTTTCCTTG GCCTTCTCA GCTTCACCTT GATACTGGGC CTCTTCTTG TCATGTCTGA	1680
	AGCTGTGGAC CAGAGACCTG GACTTTTGTC TGCTTAAGGG AAATGAGGGA AGTAAAGACA	1740
30	GTGAAGGGGT GGAGGGTTGA TCAGGGCACA GTGGACAGGG AGACCTCACA GAGAAAGGCC	1800
	TGGAAGGTGA TTCCCGTGT GACTCATGGA TAGGATACAA AATGTGTTCC ATGTACCATT	1860
	AATCTTGACA TATGCCATGC ATAAAGACTT CCTATTAAAA TAAGCTTTGG AAGAGATTAC	1920
35	ACATGATGTC TTTTCTTAG AGATTCACAG TGCATGTTAG TGTAATAAAG AGATAAGTCC	1980
	TACAGTA	2000

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 497 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

EP 0 950 711 A2

(ii) MOLECULE TYPE: protein

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(v) FRAGMENT TYPE: C-terminal

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Lys Ala Ser Gly Gln Trp Glu Ala Glu Asp Leu His Leu Asp Asp Glu
1 5 10 15

Glu Ser Ser Lys Arg Pro Leu Gly Leu Leu Ala Arg Gln Ala Glu Asn
20 25 30

His Tyr Asp Gln Asp Leu Asp Glu Leu Gln Leu Glu Met Glu Asp Ser
30 35 40 45

Lys Pro His Pro Ser Val Gln Cys Ser Pro Thr Pro Gly Pro Phe Lys
35 50 55 60

Pro Cys Glu Tyr Leu Phe Glu Ser Trp Gly Ile Arg Leu Ala Val Trp
40 65 70 75 80

Ala Ile Val Leu Leu Ser Val Leu Cys Asn Gly Leu Val Leu Leu Thr
45 85 90 95

Val Phe Ala Gly Gly Pro Ala Pro Leu Pro Pro Val Lys Phe Val Val
50 100 105 110

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	Gly	Ala	Ile	Ala	Gly	Ala	Asn	Thr	Leu	Thr	Gly	Ile	Ser	Cys	Gly	Leu
5						115				120					125	
	Leu	Ala	Ser	Val	Asp	Ala	Leu	Thr	Phe	Gly	Gln	Phe	Ser	Glu	Tyr	Gly
10						130				135					140	
	Ala	Arg	Trp	Glu	Thr	Gly	Leu	Gly	Cys	Arg	Ala	Thr	Gly	Phe	Leu	Ala
15						145				150				155		160
	Val	Leu	Gly	Ser	Glu	Ala	Ser	Val	Leu	Leu	Leu	Thr	Leu	Ala	Ala	Val
20										165				170		175
	Gln	Cys	Ser	Val	Ser	Val	Ser	Cys	Val	Arg	Ala	Tyr	Gly	Lys	Ser	Pro
25										180				185		190
	Ser	Leu	Gly	Ser	Val	Arg	Ala	Gly	Val	Leu	Gly	Cys	Leu	Ala	Leu	Ala
30										195				200		205
	Gly	Leu	Ala	Ala	Ala	Leu	Pro	Leu	Ala	Ser	Val	Gly	Glu	Tyr	Gly	Ala
35						210				215				220		
	Ser	Pro	Leu	Cys	Leu	Pro	Tyr	Ala	Pro	Pro	Glu	Gly	Gln	Pro	Ala	Ala
40						225				230				235		240
	Leu	Gly	Phe	Thr	Val	Ala	Leu	Val	Met	Met	Asn	Ser	Phe	Cys	Phe	Leu
45										245				250		255
	Val	Val	Ala	Gly	Ala	Tyr	Ile	Lys	Leu	Tyr	Cys	Asp	Leu	Pro	Arg	Gly
50										260				265		270
55																

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5	Asp Phe Glu Ala Val Trp Asp Cys Ala Met Val Arg His Val Ala Trp	275	280	285
10	Leu Ile Phe Ala Asp Gly Leu Leu Tyr Cys Pro Val Ala Phe Leu Ser	290	295	300
15	Phe Ala Ser Met Leu Gly Leu Phe Pro Val Thr Pro Glu Ala Val Lys	305	310	315
20	Ser Val Leu Leu Val Val Leu Pro Leu Pro Ala Cys Leu Asn Pro Leu	325	330	335
25	Leu Tyr Leu Leu Phe Asn Pro His Phe Arg Asp Asp Leu Arg Arg Leu	340	345	350
30	Arg Pro Arg Ala Gly Asp Ser Gly Pro Leu Ala Tyr Ala Ala Ala Gly	355	360	365
35	Glu Leu Glu Lys Ser Ser Cys Asp Ser Thr Gln Ala Leu Val Ala Phe	370	375	380
40	Ser Asp Val Asp Leu Ile Leu Glu Ala Ser Glu Ala Gly Arg Pro Pro	385	390	395
45	Gly Leu Glu Thr Tyr Gly Phe Pro Ser Val Thr Leu Ile Ser Cys Gln	405	410	415
50	Gln Pro Gly Ala Pro Arg Leu Glu Gly Ser His Cys Val Glu Pro Glu	420	425	430
55				

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Gly Asn His Phe Gly Asn Pro Gln Pro Ser Met Asp Gly Glu Leu Leu

435

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445

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Leu Arg Ala Glu Gly Ser Thr Pro Ala Gly Gly Gly Leu Ser Gly Gly

450

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460

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Gly Ala Phe Ser Pro Leu Ala Trp Pro Leu Leu His Thr Cys Lys Tyr

465

470

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480

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Pro Ser Pro Phe Phe Ser Ser Pro Leu Phe Pro Phe Leu Ser Pro Pro

485

490

495

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Arg

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2) INFORMATION FOR SEQ ID NO: 9:

30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3041 base pairs

35

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

50

ATGCGCTTGG AGGGAGAGGG CCGCTCAGCG AGGGCGGGAC AGAATCTCTC CCGGGCTGGG

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EP 0 950 711 A2

	AGTGCACGGC GCGGTGCGCC CAGGGACCTC AGCATGAACA ACCTCACAGA GCTTCAGCCT	120
	GGCCTCTTCC ACCACCTGCG CTTCTTGGAG GAGCTGCGTC TCTCTGGGAA CCATCTCTCA	180
5	CACATCCCAG GACAAGCATT CTCTGGTCTC TACAGCCTGA AAATCCTGAT GCTGCAGAAC	240
	AATCAGCTGG GAGGAATCCC CGCAGAGGCG CTGTGGGAGC TGCCGAGCCT GCAGTCGCTA	300
	GACCTGAATT ATAACAAGCT GCAGGAGTTC CCTGTGGCCA TCCGGACCCT GGGCAGACTG	360
10	CAGGAACTGG GGTTCATAA CAACAACATC AAGGCCATCC CAGAAAAGGC CTTTCATGGGG	420
	AACCTCTGTC TACAGACGAT ACACTTTTAT GATAACCCAA TCCAGTTTGT GGAAGATCG	480
	GCATTCCAGT ACCTGCCTAA ACTCCACACA CTATCTCTGA ATGGTGCCAT GGACATCCAG	540
	GAGTTTCCAG ATCTCAAAGG CACCACCAGC CTGGAGATCC TGACCCTGAC CCGCGCAGGC	600
15	ATCCGGCTGC TCCCATCGGG GATGTGCCAA CAGCTGCCCA GGCTCCGAGT CCTGGAACCTG	660
	TCTCACAATC AAATTGAGGA GCTGCCCAGC CTGCACAGGT GTCAGAAATT GGAGGAAATC	720
	GGCCTCCAAC ACAACCGCAT CTGGGAAATT GGAGCTGACA CCTTCAGCCA GCTGAGCTCC	780
20	CTGCAAGCCC TGGATCTTAG CTGGAACGCC ATCCGGTCCA TCCACCCCGA GGCCTTCTCC	840
	ACCCTGCACT CCCTGGTCAA GCTGGACCTG ACAGACAACC AGCTGACCAC ACTGCCCTCTG	900
	GCTGGACTTG GGGGCTTGAT GCATCTGAAG CTCAAAGGGA ACCTTGCTCT CTCCCAGGCC	960
25	TTCTCCAAGG ACAGTTTCCC AAAACTGAGG ATCCTGGAGG TGCCTTATGC CTACCAGTGC	1020
	TGTCCCTATG GGATGTGTGC CAGCTTCTTC AAGGCCTCTG GGCAGTGGGA GGCTGAAGAC	1080
	CTTCACCTTG ATGATGAGGA GTCTTCAAAA AGGCCCCCTGG GCCTCCTTGC CAGACAAGCA	1140
	GAGAACCACT ATGACCAGGA CCTGGATGAG CTCCAGCTGG AGATGGAGGA CTCAAAGCCA	1200
30	CACCCCACTG TCCAGTGTAG CCTACTCCA GGCCCCCTCA AGCCCTGTGA GTACCTCTTT	1260
	GAAAGCTGGG GCATCCGCCT GGCCGTGTGG GCCATCGTGT TGCTCTCCGT GCTCTGCAAT	1320
	GGACTGTGTC TGCTGACCGT GTTCGCTGGC GGGCCTGCCC CCCTGCCCCC GGTCAAGTTT	1380
35	GTGGTAGGTG CGATTGCAGG CGCCAACACC TTGACTGGCA TTTCCTGTGG CCTTCTAGCC	1440
	TCAGTCGATG CCCTGACCTT TGGTCAGTTC TCTGAGTACG GAGCCCGCTG GGAGACGGGG	1500
	CTAGGCTGCC GGGCCACTGG CTTCTGGCA GTACTTGGGT CGGAGGCATC GGTGCTGCTG	1560
40	CTCACTCTGG CCGCAGTGCA GTGCAGCGTC TCCGTCTCCT GTGTCCGGGC CTATGGGAAG	1620
	TCCCCCTCCC TGGGCAGCGT TCGAGCAGGG GTCCTAGGCT GCCTGGCACT GGCAGGGCTG	1680
	GCCGCCGCAC TGCCCTGGC CTCAGTGGGA GAATACGGGG CCTCCCCACT CTGCCTGCCC	1740
	TACGCGCCAC CTGAGGGTCA GCCAGCAGCC CTGGGCTTCA CCGTGGCCCT GGTGATGATG	1800
45	AACTCCTTCT GTTTCCTGGT CGTGGCCGGT GCCTACATCA AACTGTACTG TGACCTGCCG	1860
	CGGGGCGACT TTGAGGCCGT GTGGGACTGC GCCATGGTGA GGCACGTGGC CTGGCTCATC	1920
	TTCCGAGACG GGCTCCTCTA CTGTCCCGTG GCCTTCTCA GCTTCGCCTC CATGCTGGGC	1980
50	CTCTTCCCTG TCACGCCCGA GGCCGTCAAG TCTGTCTGTC TGGTGGTGCT GCCCCTGCCT	2040
	GCCTGCCTCA ACCCACTGCT GTACCTGCTC TTCAACCCCC ACTTCCGGGA TGACCTTCGG	2100

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5 CGGCTTCGGC CCCGCGCAGG GGAATCAGGG CCCCTAGCCT ATGCTGCGGC CGGGGAGCTG 2160
 GAGAAGAGCT CCTGTGATTC TACCCAGGCC CTGGTAGCCT TCTCTGATGT GGATCTCATT 2220
 CTGGAAGCTT CTGAAGCTGG GCGGCCCCCT GGGCTGGAGA CCTATGGCTT CCCCTCAGTG 2280
 ACCCTCATCT CCTGTACACA GCCAGGGGCC CCCAGGCTGG AGGGCAGCCA TTGTGTAGAG 2340
 CCAGAGGGGA ACCACTTTGG GAACCCCCAA CCCTCCATGG ATGGAGAACT GCTGCTGAGG 2400
 10 GCAGAGGGAT CTACGCCAGC AGGTGGAGGC TTGTCAGGGG GTGGCGCTTT CAGCCCTCTG 2460
 GCTTGGCCTT TGCTTACAC GTGTAAATAT CCCTCCCAT TCTTCTCTTC CCCTCTCTTC 2520
 CCTTCTCTCT CTCCCCCTCG GTGAATGATG GCTGCTTCTA AAACAAATAC AACCAAAACT 2580
 CAGCAGTGTG ATCTATAGCA GGATGGCCCA GTACCTGGCT CCACTGATCA CCTCTCTCCT 2640
 15 GTGACCATCA CCAACGGGTG CCCTCTTGGC CTGGCTTTCC CTGGGCCTTC CTCAGCTTCA 2700
 CCTTGATACT GGGCCTCTTC CTGTGATGT CTGAAGCTGT GGACCAGAGA CCTGGACTTT 2760
 TGTCTGCTTA AGGGAAATGA GGGAAAGTAA GACAGTGAAG GGGTGGAGGG TTGATCAGGG 2820
 20 CACAGTGGAC AGGGAGACCT CACAGAGAAA GGCCTGGAAG GTGATTTCCC GTGTGACTCA 2880
 TGGATAGGAT ACAAATGTG TTCCATGTAC CATTAATCTT GACATATGCC ATGCATAAAG 2940
 ACTTCTTATT AAAATAAGCT TTGAAGAGA TTACACATGA TGTCTTTTTC TTAGAGATTC 3000
 25 ACAGTGCATG TTAGTGTAAT AAAGAGATAA GTCCTACAGT A 3041

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 847 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

EP 0 950 711 A2

Met Arg Leu Glu Gly Glu Gly Arg Ser Ala Arg Ala Gly Gln Asn Leu
1 5 10 15

Ser Arg Ala Gly Ser Ala Arg Arg Gly Ala Pro Arg Asp Leu Ser Met
20 25 30

Asn Asn Leu Thr Glu Leu Gln Pro Gly Leu Phe His His Leu Arg Phe
35 40 45

Leu Glu Glu Leu Arg Leu Ser Gly Asn His Leu Ser His Ile Pro Gly
50 55 60

Gln Ala Phe Ser Gly Leu Tyr Ser Leu Lys Ile Leu Met Leu Gln Asn
65 70 75 80

Asn Gln Leu Gly Gly Ile Pro Ala Glu Ala Leu Trp Glu Leu Pro Ser
85 90 95

Leu Gln Ser Leu Asp Leu Asn Tyr Asn Lys Leu Gln Glu Phe Pro Val
100 105 110

Ala Ile Arg Thr Leu Gly Arg Leu Gln Glu Leu Gly Phe His Asn Asn
115 120 125

Asn Ile Lys Ala Ile Pro Glu Lys Ala Phe Met Gly Asn Pro Leu Leu
130 135 140

Gln Thr Ile His Phe Tyr Asp Asn Pro Ile Gln Phe Val Gly Arg Ser
145 150 155 160

Ala Phe Gln Tyr Leu Pro Lys Leu His Thr Leu Ser Leu Asn Gly Ala
165 170 175

EP 0 950 711 A2

Met Asp Ile Gln Glu Phe Pro Asp Leu Lys Gly Thr Thr Ser Leu Glu
5 180 185 190

Ile Leu Thr Leu Thr Arg Ala Gly Ile Arg Leu Leu Pro Ser Gly Met
10 195 200 205

Cys Gln Gln Leu Pro Arg Leu Arg Val Leu Glu Leu Ser His Asn Gln
15 210 215 220

Ile Glu Glu Leu Pro Ser Leu His Arg Cys Gln Lys Leu Glu Glu Ile
20 225 230 235 240

Gly Leu Gln His Asn Arg Ile Trp Glu Ile Gly Ala Asp Thr Phe Ser
25 245 250 255

Gln Leu Ser Ser Leu Gln Ala Leu Asp Leu Ser Trp Asn Ala Ile Arg
30 260 265 270

Ser Ile His Pro Glu Ala Phe Ser Thr Leu His Ser Leu Val Lys Leu
35 275 280 285

Asp Leu Thr Asp Asn Gln Leu Thr Thr Leu Pro Leu Ala Gly Leu Gly
40 290 295 300

Gly Leu Met His Leu Lys Leu Lys Gly Asn Leu Ala Leu Ser Gln Ala
45 305 310 315 320

Phe Ser Lys Asp Ser Phe Pro Lys Leu Arg Ile Leu Glu Val Pro Tyr
50 325 330 335

Ala Tyr Gln Cys Cys Pro Tyr Gly Met Cys Ala Ser Phe Phe Lys Ala
55 340 345 350

EP 0 950 711 A2

5 Ser Gly Gln Trp Glu Ala Glu Asp Leu His Leu Asp Asp Glu Glu Ser
 355 360 365
 10 Ser Lys Arg Pro Leu Gly Leu Leu Ala Arg Gln Ala Glu Asn His Tyr
 370 375 380
 15 Asp Gln Asp Leu Asp Glu Leu Gln Leu Glu Met Glu Asp Ser Lys Pro
 385 390 395 400
 20 His Pro Ser Val Gln Cys Ser Pro Thr Pro Gly Pro Phe Lys Pro Cys
 405 410 415
 25 Glu Tyr Leu Phe Glu Ser Trp Gly Ile Arg Leu Ala Val Trp Ala Ile
 420 425 430
 30 Val Leu Leu Ser Val Leu Cys Asn Gly Leu Val Leu Leu Thr Val Phe
 435 440 445
 35 Ala Gly Gly Pro Ala Pro Leu Pro Pro Val Lys Phe Val Val Gly Ala
 450 455 460
 40 Ile Ala Gly Ala Asn Thr Leu Thr Gly Ile Ser Cys Gly Leu Leu Ala
 465 470 475 480
 45 Ser Val Asp Ala Leu Thr Phe Gly Gln Phe Ser Glu Tyr Gly Ala Arg
 485 490 495
 50 Trp Glu Thr Gly Leu Gly Cys Arg Ala Thr Gly Phe Leu Ala Val Leu
 500 505 510
 55 Gly Ser Glu Ala Ser Val Leu Leu Leu Thr Leu Ala Ala Val Gln Cys
 515 520 525

EP 0 950 711 A2

5 Ser Val Ser Val Ser Cys Val Arg Ala Tyr Gly Lys Ser Pro Ser Leu
 530 535 540
 Gly Ser Val Arg Ala Gly Val Leu Gly Cys Leu Ala Leu Ala Gly Leu
 545 550 555 560
 10 Ala Ala Ala Leu Pro Leu Ala Ser Val Gly Glu Tyr Gly Ala Ser Pro
 565 570 575
 15 Leu Cys Leu Pro Tyr Ala Pro Pro Glu Gly Gln Pro Ala Ala Leu Gly
 580 585 590
 20 Phe Thr Val Ala Leu Val Met Met Asn Ser Phe Cys Phe Leu Val Val
 595 600 605
 25 Ala Gly Ala Tyr Ile Lys Leu Tyr Cys Asp Leu Pro Arg Gly Asp Phe
 610 615 620
 30 Glu Ala Val Trp Asp Cys Ala Met Val Arg His Val Ala Trp Leu Ile
 625 630 635 640
 35 Phe Ala Asp Gly Leu Leu Tyr Cys Pro Val Ala Phe Leu Ser Phe Ala
 645 650 655
 40 Ser Met Leu Gly Leu Phe Pro Val Thr Pro Glu Ala Val Lys Ser Val
 660 665 670
 45 Leu Leu Val Val Leu Pro Leu Pro Ala Cys Leu Asn Pro Leu Leu Tyr
 675 680 685
 50 Leu Leu Phe Asn Pro His Phe Arg Asp Asp Leu Arg Arg Leu Arg Pro
 690 695 700
 55

EP 0 950 711 A2

5 Arg Ala Gly Asp Ser Gly Pro Leu Ala Tyr Ala Ala Ala Gly Glu Leu
705 710 715 720

10 Glu Lys Ser Ser Cys Asp Ser Thr Gln Ala Leu Val Ala Phe Ser Asp
725 730 735

15 Val Asp Leu Ile Leu Glu Ala Ser Glu Ala Gly Arg Pro Pro Gly Leu
740 745 750

20 Glu Thr Tyr Gly Phe Pro Ser Val Thr Leu Ile Ser Cys Gln Gln Pro
755 760 765

25 Gly Ala Pro Arg Leu Glu Gly Ser His Cys Val Glu Pro Glu Gly Asn
770 775 780

30 His Phe Gly Asn Pro Gln Pro Ser Met Asp Gly Glu Leu Leu Leu Arg
785 790 795 800

35 Ala Glu Gly Ser Thr Pro Ala Gly Gly Gly Leu Ser Gly Gly Gly Ala
805 810 815

40 Phe Ser Pro Leu Ala Trp Pro Leu Leu His Thr Cys Lys Tyr Pro Ser
820 825 830

45 Pro Phe Phe Ser Ser Pro Leu Phe Pro Phe Leu Ser Pro Pro Arg
835 840 845

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 279 base pairs

(B) TYPE: nucleic acid

EP 0 950 711 A2

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

20

```
TCCAGAATAA TCAGTTGAAA ACAGTACCCA GTGAAGCCAT TCGAGGGCTG AGTGCTTTGC      60
AGTCTTTGNG TTTAGATGCC AACCATATTA CCTNAGTCCC CGAGGACAGT TTTGAAGGAC      120
TTGTTTCAGTT ACGGCATCTG TGGCTGGATG ACAACAGCTT GACGGAGGTG CCTGTGCACC      180
NCCTCAGCAA TCTGCCCACC CTACAGGCGC TGANCCTGGC TCTCAACAAG ATCTCAAGNA      240
TCCCTGACTT TGCATTTACC AACCTTTCAA GCCTGGTAG                               279
```

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(2) INFORMATION FOR SEQ ID NO: 12:

30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 284 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: cDNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

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```
CAACAACATC AAGGCCATCC CAGAAAAGGC CTTTCATGGG AACCCCTCTGC TACAGACGAT      60
ACACTTTTAT GATAACCCAA TCCAGTTTGT GGAAGATCG GCATTCCAGT ACCTGCCTAA      120
ACTCCACACA CTATCTCTGA ATGGTGCCAT GGACATCCAG GAGTTTCCAG ATCTCAAAGG      180
```

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CACCACCAGC CTGGAGATCC TGACCCTGAC CCGCGCAGGC ATCCGGCTGC TCCCATCGGG 240
 GATGTGCCAA CAGCTGCCCA GGCTCCGAGT CCTGTGAGTG CNAA 284

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 764 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GCAGTGGCTG CAAAGTAGCT GGGTTTCTTG CAGTTTCTC CTCAGAAAGT GCCATATTTT 60
 TATTAATGCT AGCAACTGTC GAAAGANGCT TATCTGCAA AGATATAATG AAAAATGGGA 120
 AGAGCAATCA TCTCAAACAG TTCCGGGTTG CTGCCCTTTT GGCTTTCCTA GGTGCTACAG 180
 TAGCAGGCTG TTTTCCCCTT TTCCATAGAG GGGAATATTC TGCATCACCC CTTTGTTTGC 240
 CATTTCCTAC AGGTGAAACG CCATCATTAG GATTCAGTGT AACGTTAGTG NTATTAANCT 300
 CACTAGCATT TTTATTAATG GCCGTTATCT AACTAAGCT ATACTGCAAC TTGGAAAANG 360
 AGGACCTCTC AGAAAACCTCA CAATCTAGCA TGATTAAGCA TGTCGCTTGG CTAATCTTCA 420
 CCAATTGCAT CTTTTTCTGC CCTGTGGCGT TTTTTTCATT TGCACCATTG ATCACTGCAA 480
 TCTCTATCAG CCCCAGAAATA ATGAAGTCTG TTA CTCTGAT ATTTTTTCCA TTGCCTGCTT 540
 GCCTGAATCC AGTCCTGTAT GTTTTCTTCA ACCCAAAGT TAAAGAAGAC TGGAAGTTAC 600
 TGAAGCGACG TGTACCAAG AAAAGTGGAT CAGTTTCAGT TTCCATCAGT AGCCAAGGTG 660
 GTTGCTGGA ACAGGATTTC TACTACGACT GTGGCATGTA CTCACATTG CAGGGCAACC 720
 TGACTGTTTGC GACTGCTGC GAATCGTTTC TTTTAACAAA GCCA 764

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 92 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION:1..277

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Gln Asn Asn Gln Leu Lys Thr Val Pro Ser Glu Ala Ile Arg Gly Leu
1 5 10

Ser Ala Leu Gln Ser Leu Xaa Leu Asp Ala Asn His Ile Thr Xaa Val
15 20 25 30

Pro Glu Asp Ser Phe Glu Gly Leu Val Gln Leu Arg His Leu Trp Leu
35 40 45

Asp Asp Asn Ser Leu Thr Glu Val Pro Val His Xaa Leu Ser Asn Leu
50 55 60

Pro Thr Leu Gln Ala Leu Xaa Leu Ala Leu Asn Lys Ile Ser Xaa Ile
65 70 75

EP 0 950 711 A2

Pro Asp Phe Ala Phe Thr Asn Leu Ser Ser Leu Val
80 85 90

5

(2) INFORMATION FOR SEQ ID NO: 15:

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 91 amino acids

(B) TYPE: amino acid

15

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: C-terminal

25

(ix) FEATURE:

(A) NAME/KEY: Protein

30

(B) LOCATION: 1..273

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Asn Asn Ile Lys Ala Ile Pro Glu Lys Ala Phe Met Gly Asn Pro Leu

1 5 10 15

40

Leu Gln Thr Ile His Phe Tyr Asp Asn Pro Ile Gln Phe Val Gly Arg

20 25 30

45

Ser Ala Phe Gln Tyr Leu Pro Lys Leu His Thr Leu Ser Leu Asn Gly

35 40 45

50

Ala Met Asp Ile Gln Glu Phe Pro Asp Leu Lys Gly Thr Thr Ser Leu

50 55 60

55

EP 0 950 711 A2

Glu Ile Leu Thr Leu Thr Arg Ala Gly Ile Arg Leu Leu Pro Ser Gly

65 70 75

5

Met Cys Gln Gln Leu Pro Arg Leu Arg Val Leu

80 85 90

10

(2) INFORMATION FOR SEQ ID NO: 16:

15

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 254 amino acids

(B) TYPE: amino acid

20

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

30

(ix) FEATURE:

35

(A) NAME/KEY: Protein

(B) LOCATION:1

40

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

45

Ser Gly Cys Lys Val Ala Gly Phe Leu Ala Val Phe Ser Ser Glu Ser

1 5 10

50

Ala Ile Phe Leu Leu Met Leu Ala Thr Val Glu Arg Xaa Leu Ser Ala

15 20 25 30

55

EP 0 950 711 A2

5 Lys Asp Ile Met Lys Asn Gly Lys Ser Asn His Leu Lys Gln Phe Arg
 35 40 45

 10 Val Ala Ala Leu Leu Ala Phe Leu Gly Ala Thr Val Ala Gly Cys Phe
 50 55 60

 15 Pro Leu Phe His Arg Gly Glu Tyr Ser Ala Ser Pro Leu Cys Leu Pro
 65 70 75

 20 Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val Thr Leu Val
 80 85 90

 25 Xaa Leu Xaa Ser Leu Ala Phe Leu Leu Met Ala Val Ile Tyr Thr Lys
 95 100 105 110

 30 Leu Tyr Cys Asn Leu Glu Xaa Glu Asp Leu Ser Glu Asn Ser Gln Ser
 115 120 125

 35 Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe
 130 135 140

 40 Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile
 145 150 155

 45 Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro
 160 165 170

 50 Leu Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys
 175 180 185 190

 55 Phe Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser
 195 200 205

Gly Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys Leu Glu Gln

210

215

220

Asp Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln Gly Asn Leu

225

230

235

Thr Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro

240

245

250

Claims

1. An isolated polynucleotide comprising one of the sequences selected from the group of polynucleotides encoding SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:15 or SEQ ID NO:16.
2. The polynucleotide according to claim 1, said polynucleotide comprising the sequences SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 or the sequences extending from nucleotides 2-1487 from SEQ ID NO:7 or from nucleotides 1-2541 of SEQ ID NO:9.
3. A recombinant expression vector comprising the DNA according to claims 1 or 2.
4. Protein encoded by the polynucleotide according to claims 1 or 2 or the expression vector according to claim 3.
5. A cell transfected with DNA according to claims 1 or 2 or the expression vector according to claim 3.
6. A cell according to claim 5 which is a stable transfected cell which expresses the receptor protein according to claims 4.
7. Use of a DNA according to claims 1 or 2 or a expression vector according to claim 3, a cell according to claims 5 or 6 or a protein according to claim 4 in a screening assay for identification of new drugs.
8. A method for identifying ligands for the protein according to claim 4, said method comprising the steps of
 - introducing into a suitable host cell a DNA according to claims 1, 2 or an expression vector according to claims 3;
 - culturing the host cells under conditions to allow expression of the introduced DNA sequence;
 - optionally isolating the expression product;
 - bringing the host cell from the second step or the expression product from the third step into contact with potential ligands which will possibly bind to the ligand-binding domain of the expressed protein encoded by said DNA from the first step;
 - establishing the amount of binding of the ligand to the expressed protein or its signal transduction capacity.

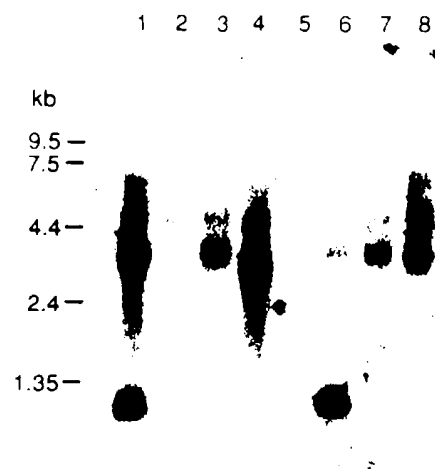


Figure 1.

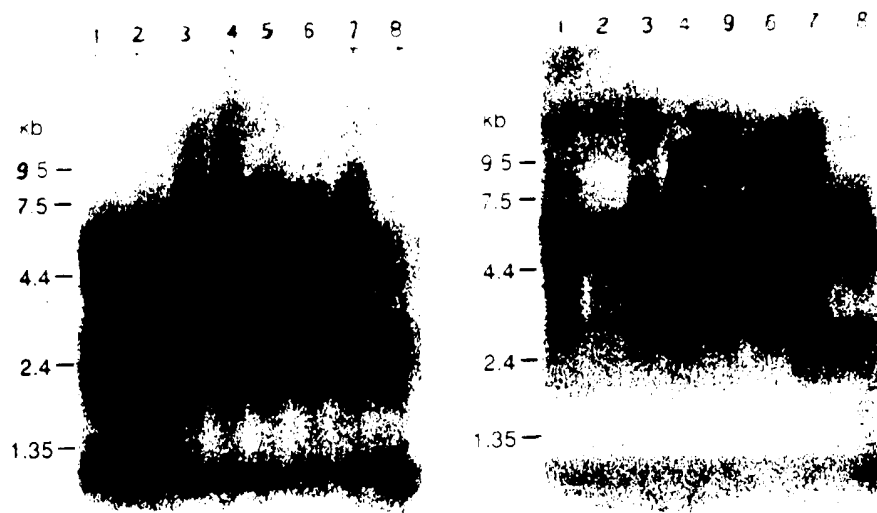


Figure 2



Figure 3